

Targeting B-Cell Receptor Signaling: Pause for MRD as a Required Endpoint

John C. Byrd, M.D.

D Warren Brown Chair of Leukemia Research

Professor of Medicine and Medicinal Chemistry

Director, Division of Hematology, Department of Medicine

The Ohio State University Comprehensive Cancer Center



The James

Ohio State is a Comprehensive Cancer Center
designated by the National Cancer Institute

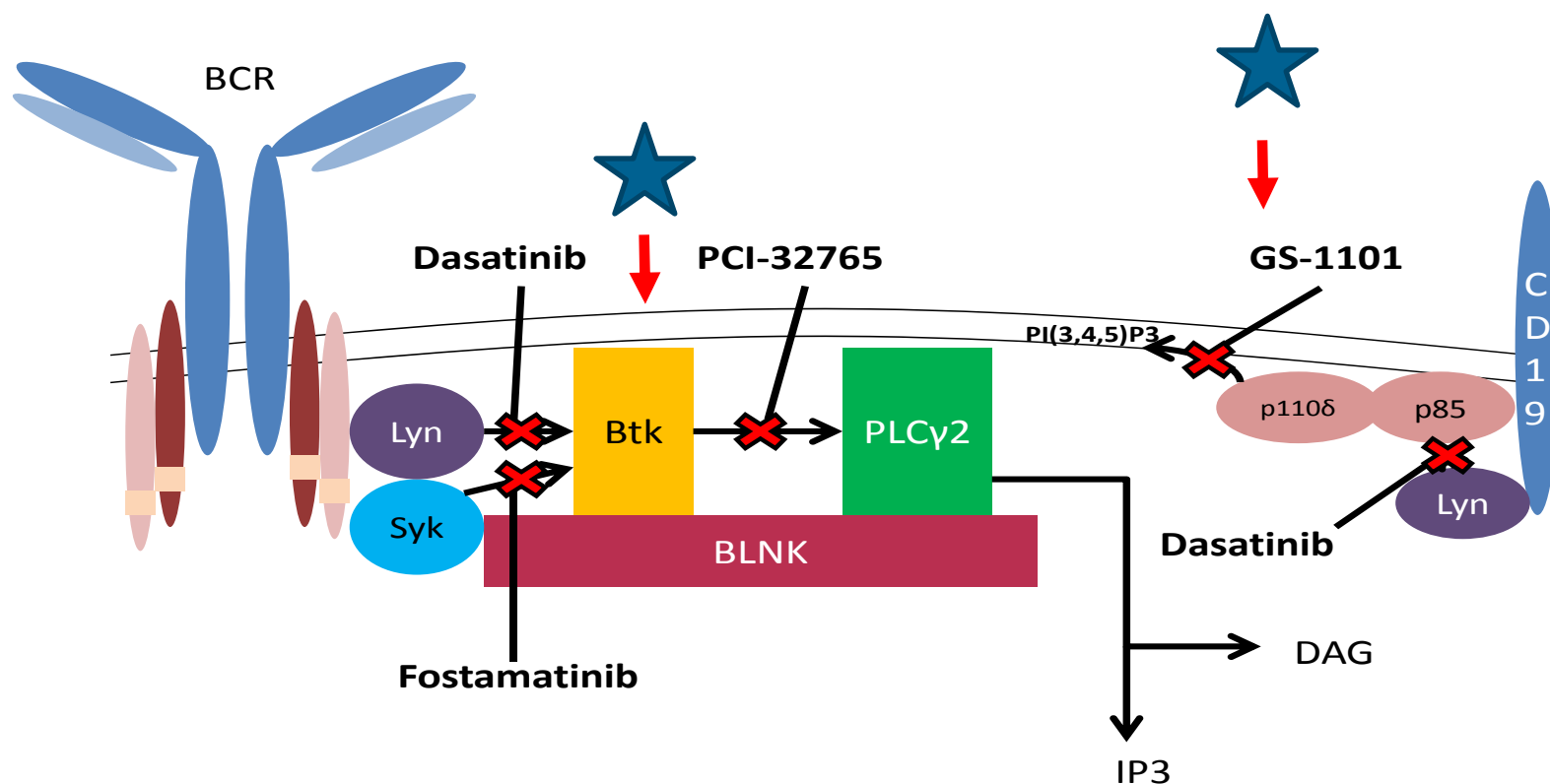
Ohio State is a Comprehensive Cancer Center
designated by the National Cancer Institute

The Ohio State University Comprehensive Cancer Center
Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

Presenter Disclosure Information

- The following relationships exist as a potential conflict of interest related to this presentation
 - « Dr. Byrd has served as an un-paid consultant for Genentech, Xencor, Merck, Pharmacyclics, Emergent Biosciences and Gilead
 - « Dr. Byrd has been a consultant for Calistoga and has residual milestone payments for success of GS-1101. These have been contractually committed to charity.
 - « Dr. Byrd is a consultant for Tragara Pharmaceuticals and has stock options in this company. These have been contractually committed to charity.

Efforts to Target BCR Signaling in CLL



Adapted: Woyach J et al: Blood 2012

Early Attempts at Targeting BCR Signaling

■ Fostamatinib

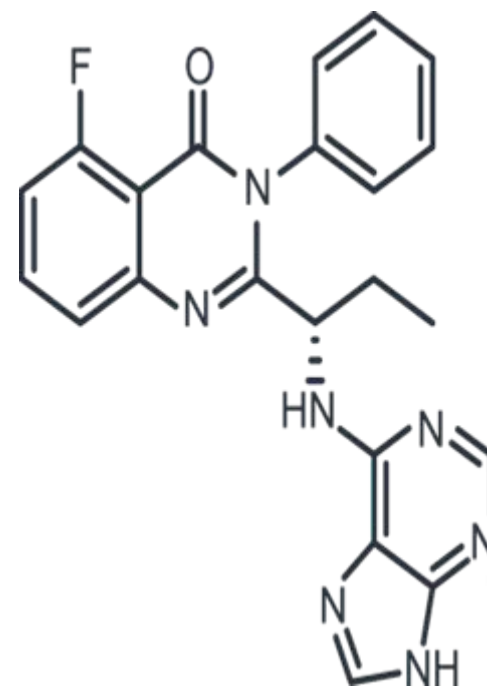
- reversible inhibitor of Syk kinase and multiple alternative kinases.
- Phase I/II study included 11 pts with CLL/SLL with PR in 6 pts with a PFS of 6.4 months.
- All patients with CLL/SLL exhibited an initial lymphocytosis believed to be due to disruption of CXCR4-SDF1 and other adhesion factors
- Toxicity acceptable—being developed in NHL and RA

■ Dasatinib

- Reversible pan-Src kinase inhibitor which also inhibits Lyn and a variety of other kinases
- Phase II trial in relapsed CLL included 15 pts with CLL having 4 PR with these lasting > 12 months
- Myelosuppression problematic

CAL-101/GS-1101

- **Selective orally available PI3K- δ inhibitor**
- **Initial phase I dosing done in healthy volunteers with favorable human PK**
- **Target inhibition shown in vivo at 50-100 η M concentrations**
- **Pre-clinical studies prompt initial development in CLL and NHL**



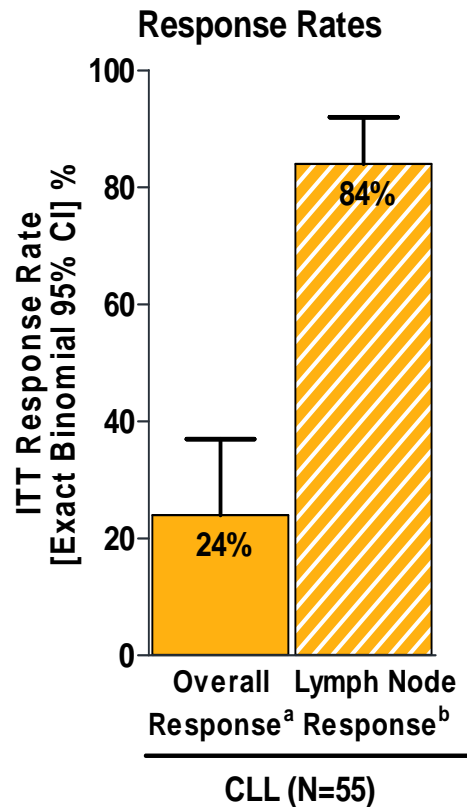
Herman S et al: Blood 2010
Lanutti B, et al: Blood 2011

GS-1101 (CAL-101) Phase I Study

- Enrolled multiple types of lymphoma and CLL in dose escalations with revision to include low-grade NHL, CLL, and mantle cell lymphoma
- Expansion cohorts in AML, multiple myeloma, CLL, NHL
- Eventual dose (150 mg BID) for phase II studies in CLL among doses explored (50-350 mg BID) included 5-12 pts at each level (total n=55) and based upon:
 - Pharmacokinetic findings—non-linear above 150 mg BID
 - Toxicity observed (transaminitis) although infrequent in CLL vs NHL
 - Efficacy in CLL—best observed at 150 mg BID and above
- CLL patients in this trial were heavily pre-treated (median prior Rx 5 (range 2-15) with 82% having bulky disease and 31% del(17p)

Coutre S, et al: ASCO 2011
To be updated ASCO 2013

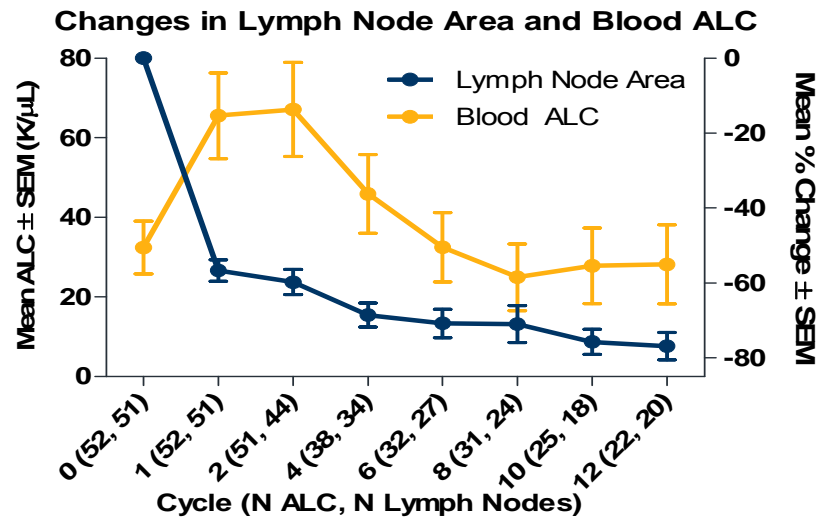
GS-1101 Phase I Results in CLL



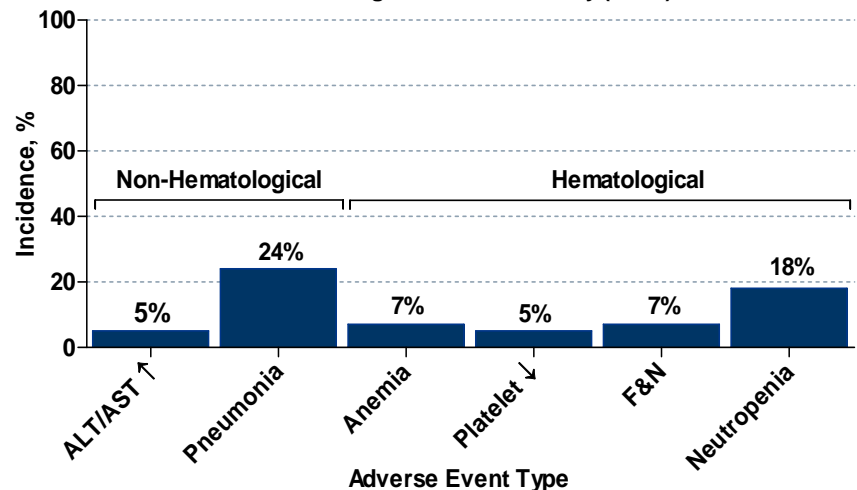
^a IWCLL response criteria

^b Decrease by 50% in the nodal SPD

Hallek, Blood June 2008



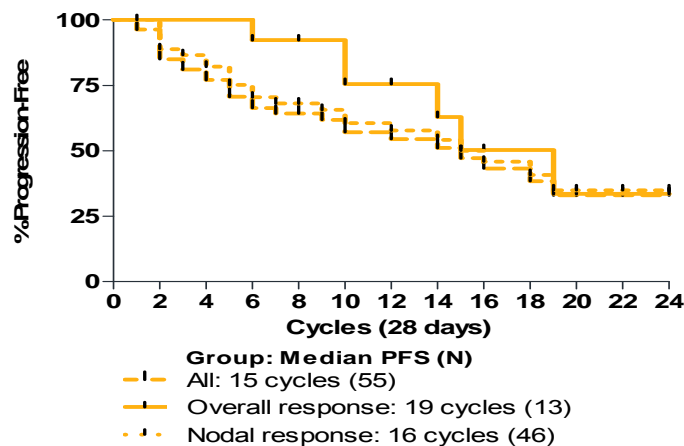
Grade 3-4 Adverse Events Occurring in ≥5% of Patients Regardless of Causality (N=55)



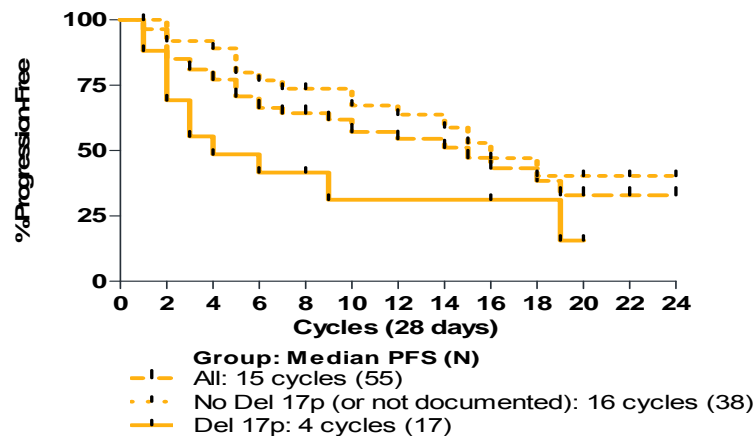
Coutre S, et al: ASCO 2011

GS-1101 Progression Free Survival

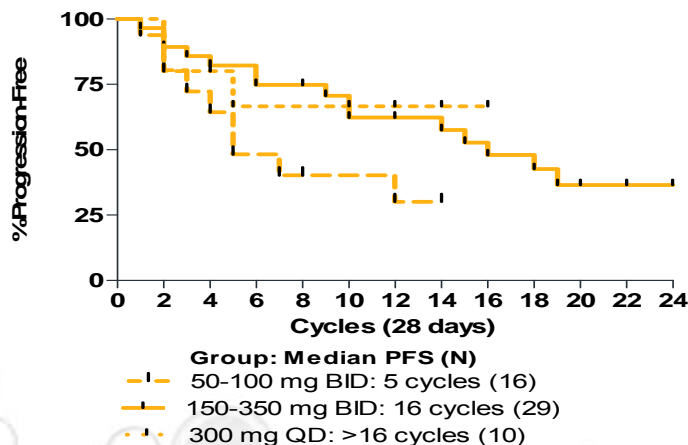
PFS -- Overall and by Response Category



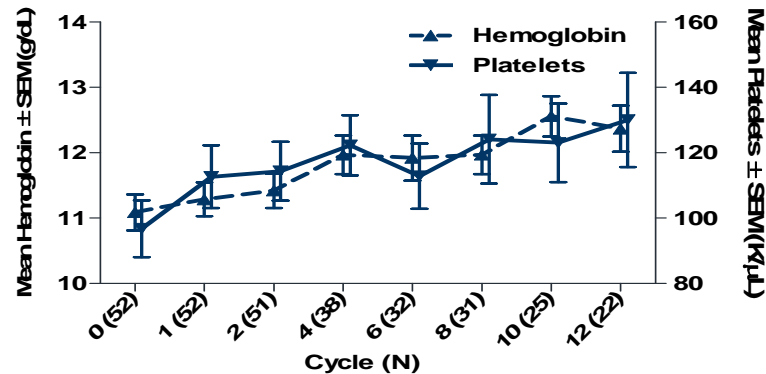
PFS -- Overall and by 17p Deletion



PFS -- Overall and by CAL-101/GS-1101 Dose

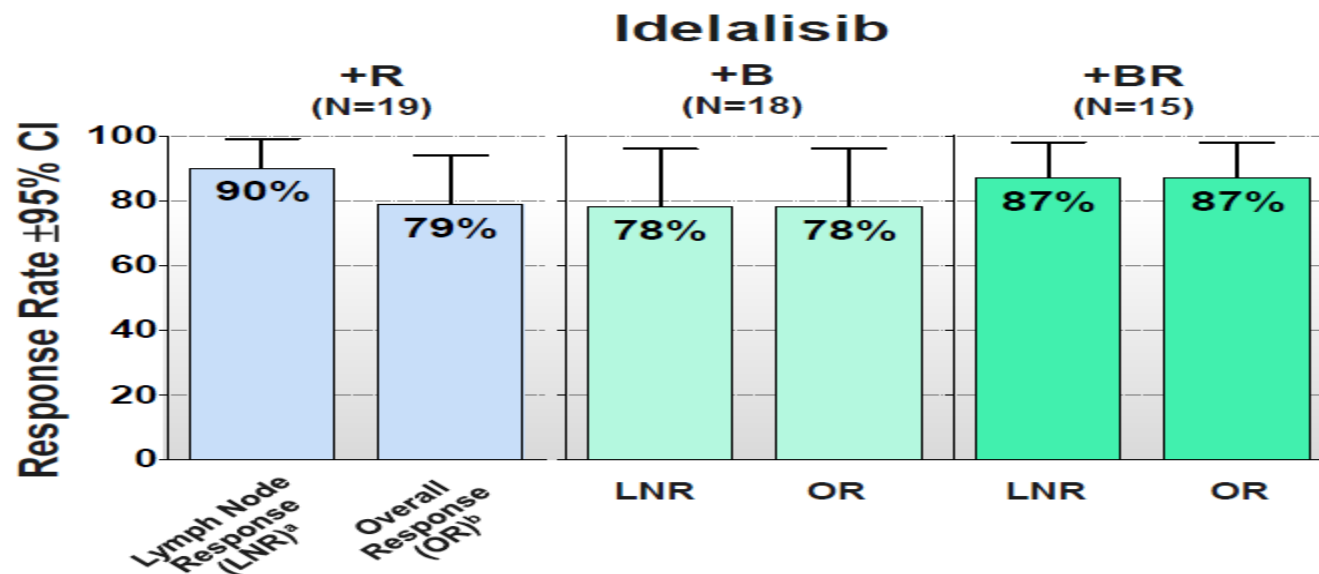
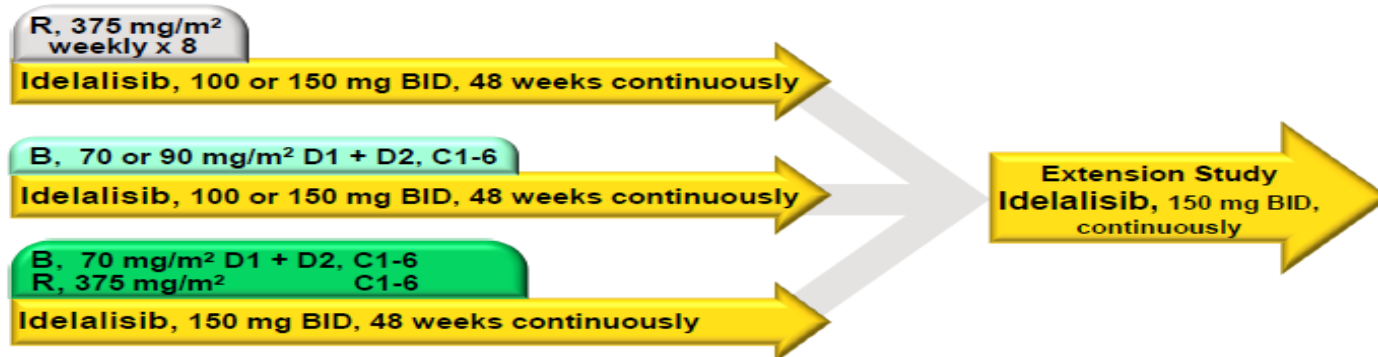


Hemoglobin and Platelet Counts



Coutre S, et al: ASCO 2011

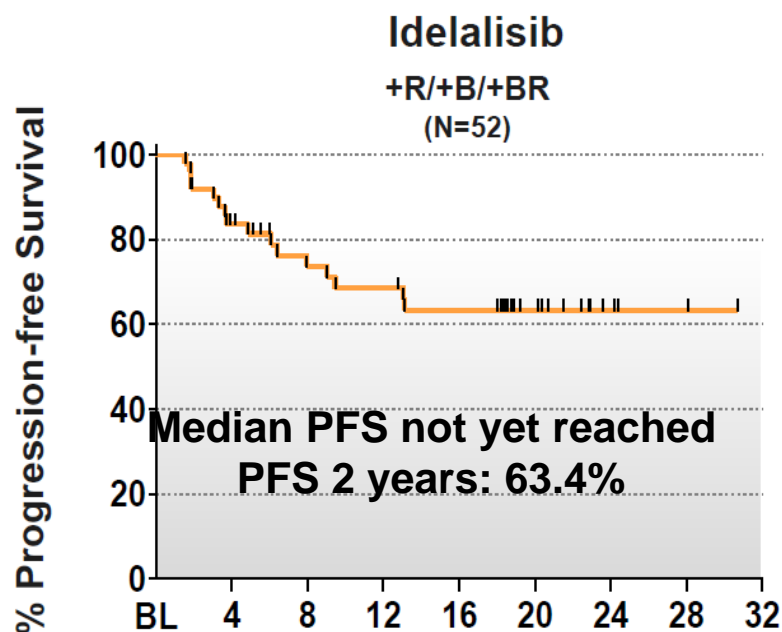
GS-1101 (Idelalisib; CAL-101) in Relapsed/Refractory CLL



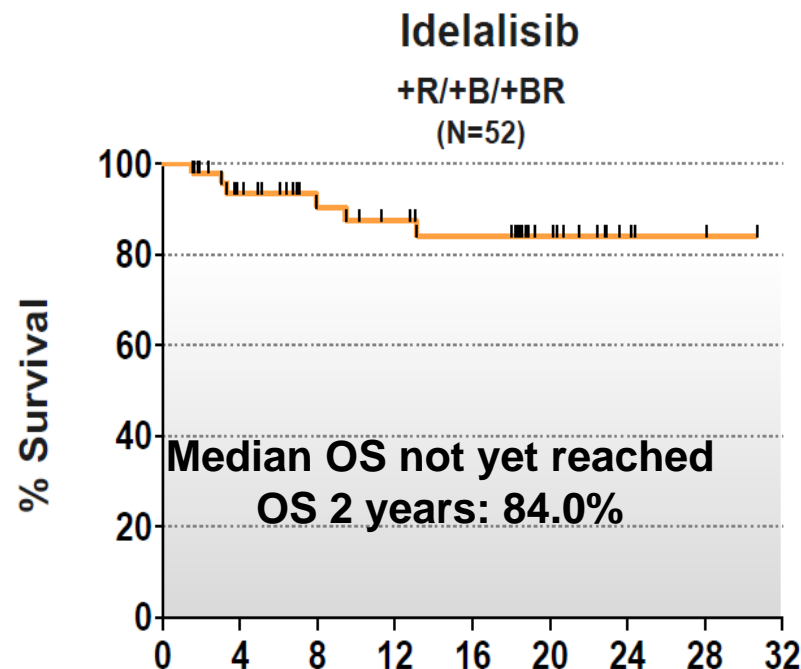
No added toxicity with GS-1101 addition

Coutre S, et al: ASH 2012

GS-1101 (Idelalisib; CAL-101) in Relapsed/Refractory CLL



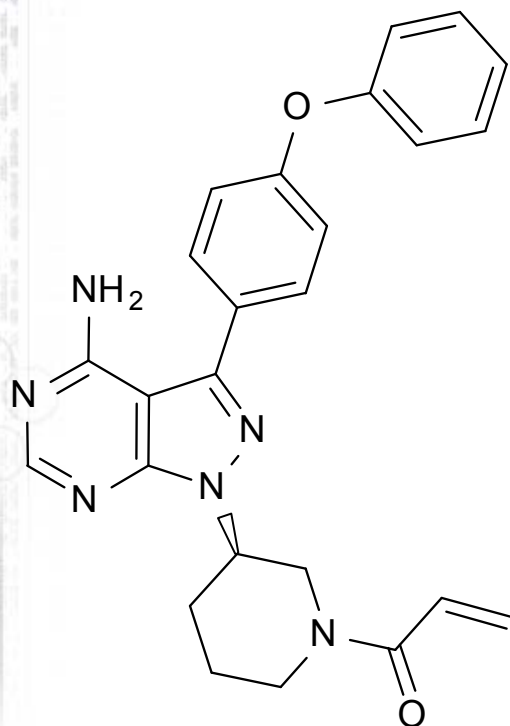
PFS



OS

Coutre S, et al: ASH 2012

Ibrutinib: A Potent Btk Inhibitor



- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent irreversible Btk inhibition with $IC_{50} = 0.5$ nM
- Orally available with daily dosing resulting in 24-hr target inhibition
- In CLL antagonizes internal and external survival and proliferation signals essential to pathogenesis

Honigberg LA et al: Proc Natl Acad Sci U S A.107:13075-80, 2010
Herman, Johnson and Byrd Blood.117:6287, 2011
de Rooij and Spaargaren Blood, 119:2590, 2012
Ponader and Burger Blood.119:1182, 2012

Ibrutinib Phase I Study in B-cell NHL

- Phase I dose escalation of ibrutinib using two schedules: 28d on, 7 d off and once-daily continuous dosing using standard 3 x 3 phase I design
- Dose escalation proceeded until MTD was achieved or three dose levels above full BTK occupancy by ibrutinib using a novel probe-based PD assay
- Eligible patients had
 - NHL or CLL with 1 but not > 4 prior therapies
 - ECOG PS ≤ 1
 - ANC > 1.5 and plts > 75 unless marrow involvement, intact renal and hepatic function
 - No secondary malignancy

Advani and Fowler J Clin Oncol 31:88-94, 2013

Results of Ibrutinib Phase I Study

- Five cohorts treated with 28 d on, 7 d off (1.25 to 12.5 mg/kg dose) and two cohorts with continuous dosing (8.3 mg/kg or fixed dose 560 mg) QD
- 56 patients treated with demographics that include
 - Median age: 65 years
 - Median prior therapies: 3 (range 1-10)
 - 93% prior rituximab/84% prior alkylator
- Histology of follicular lymphoma (16), CLL/SLL (16), mantle cell lymphoma (9), DLBCL (7), marginal zone lymphoma (4), and Waldenstrom's (4)
- Median number of cycles administered: 5

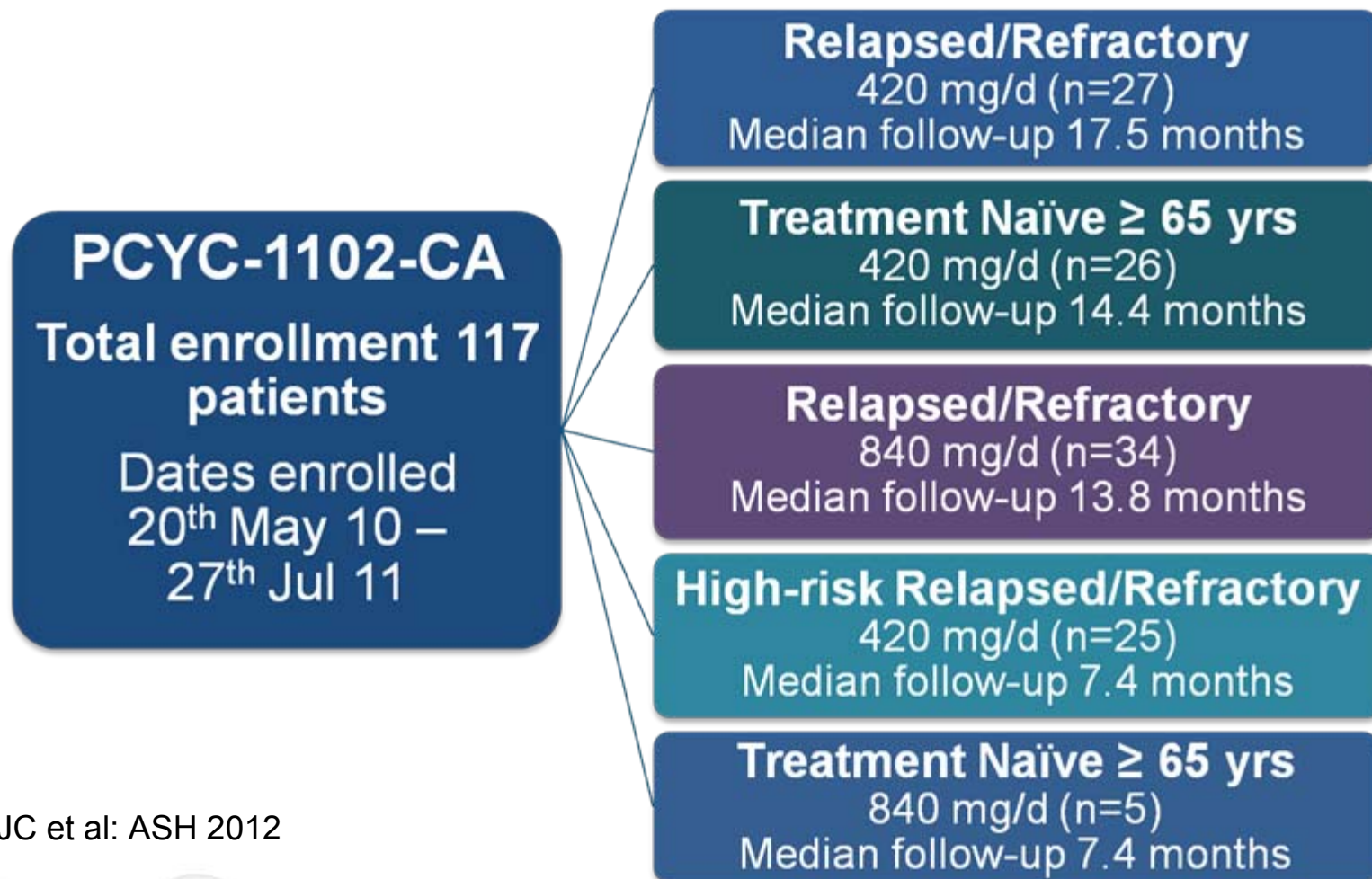
Advani and Fowler J Clin Oncol 31:88-94, 2013

Efficacy of Ibrutinib Phase I Study

- Of 56 pts enrolled on this study, 54% attained a PR or CR
 - CLL/SLL (11 of 16 including 2 CRs)
 - Follicular lymphoma (6 of 16, 3 PR)
 - Mantle cell lymphoma (7 of 9, 3 CR)
 - Large cell lymphoma (2 of 7)
 - Waldenstrom's (3 of 4)
 - Marginal zone lymphoma (1 of 4)
- Median PFS of 13.6 months for all patients, with 20 still on ibrutinib with continued response
- Early lymphocytosis with concomitant reduction in lymph nodes noted in CLL (and select MCL) pts

Advani and Fowler J Clin Oncol 31:88-94, 2013

PCYC-1102-CA: Phase IB/II in CLL/SLL

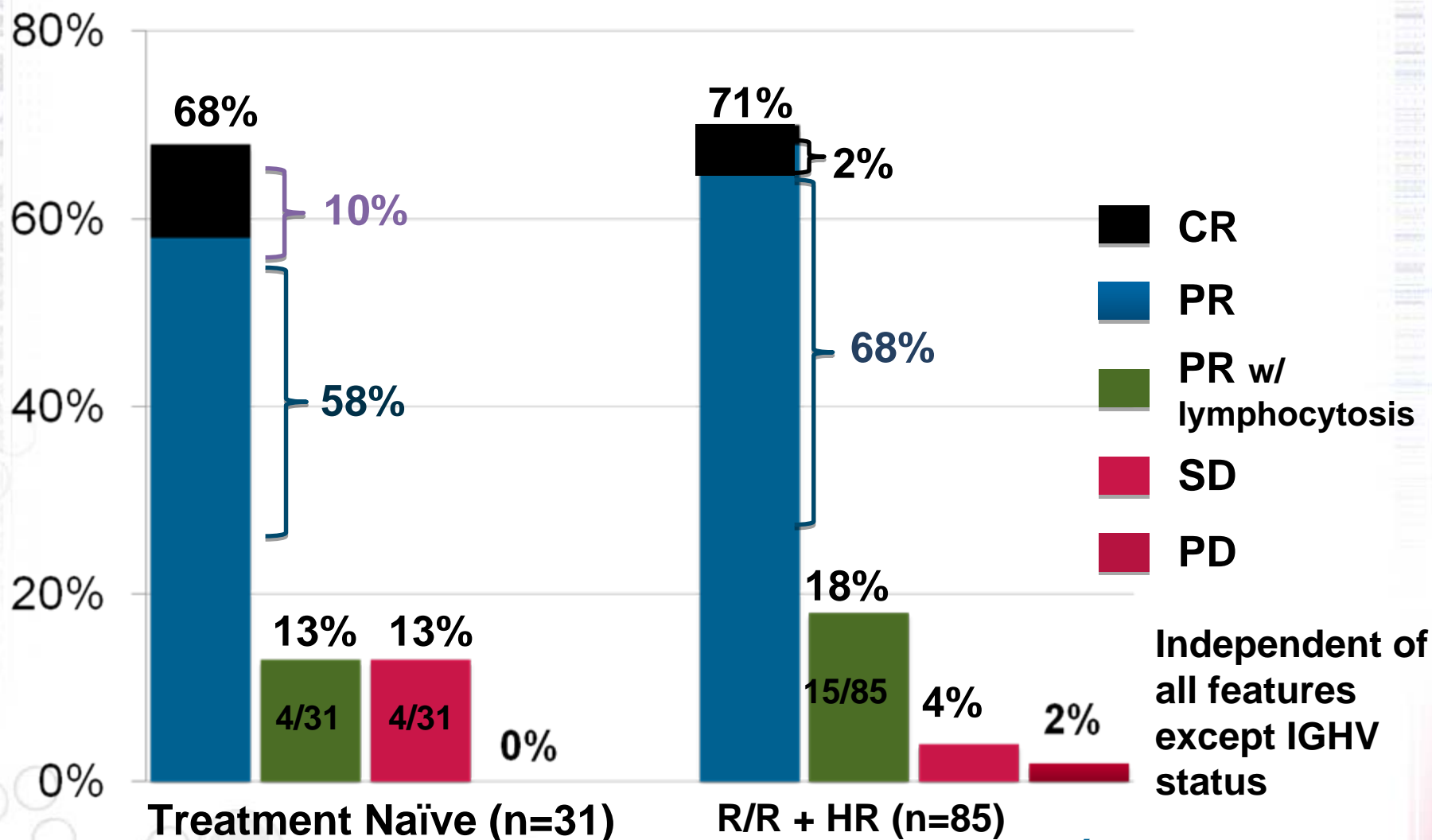


Byrd JC et al: ASH 2012

Patient Characteristics

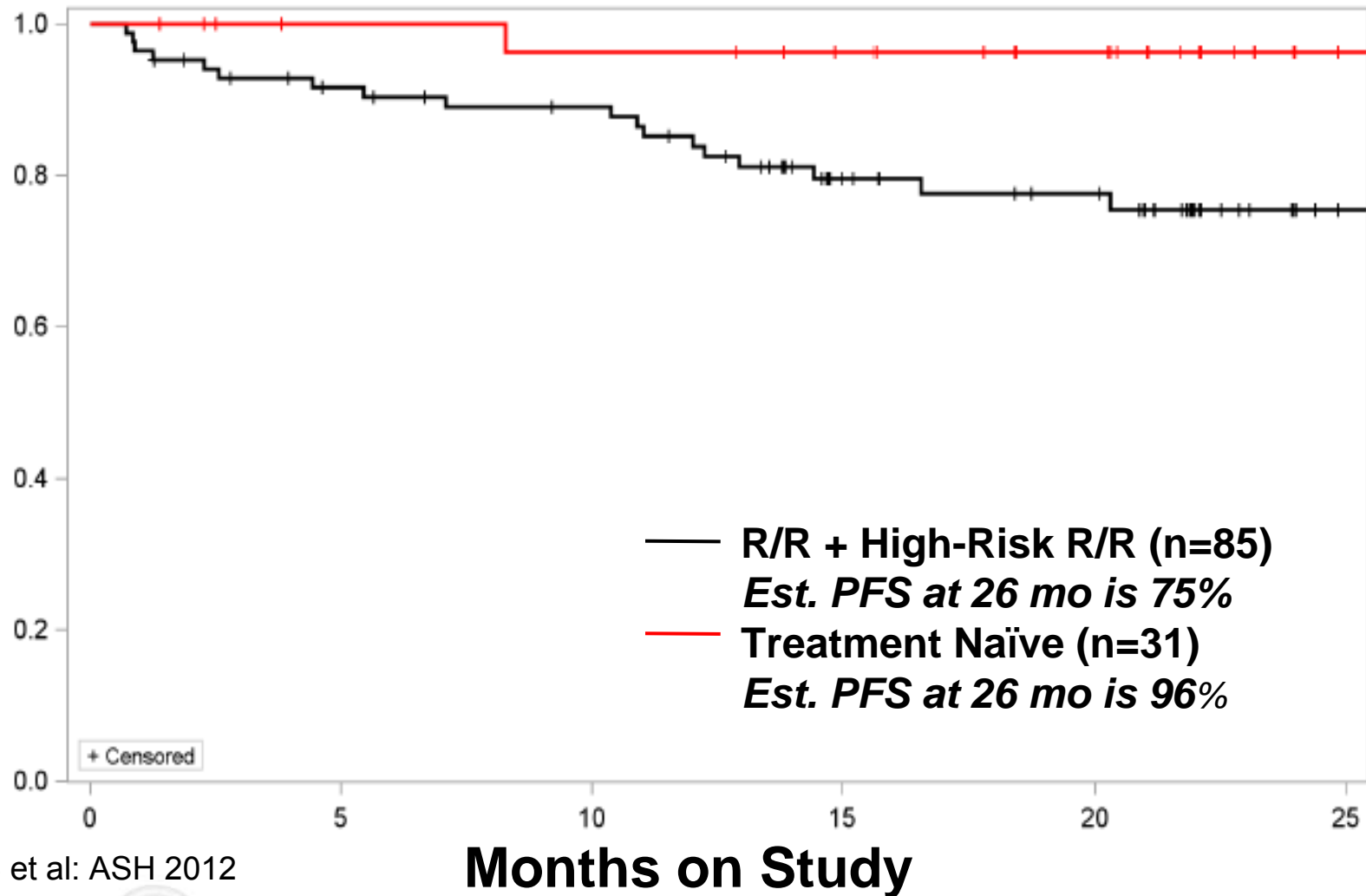
	TN \geq 65 yrs (N=31)	R/R + HR (N=85)
Age, years		
Median (Range)	71 (65 – 84)	66 (37 – 82)
\geq 70 years, (%)	74%	35%
ECOG Status		
0, 1, 2	74%, 26%, 0%	41%, 56%, 2%
Median Prior Therapies	N	4 (1-12)
β_2 Microglobulin > 3mg/L, %	26%	49%
Rai Stage III/IV at Baseline	48%	65%
Prognostic Markers, %		
IgV _H unmutated	55%	85%
del(17p13.1)	7%	35%
del(11q22.3)	3%	39%

Response by IWCLL 2008 Criteria



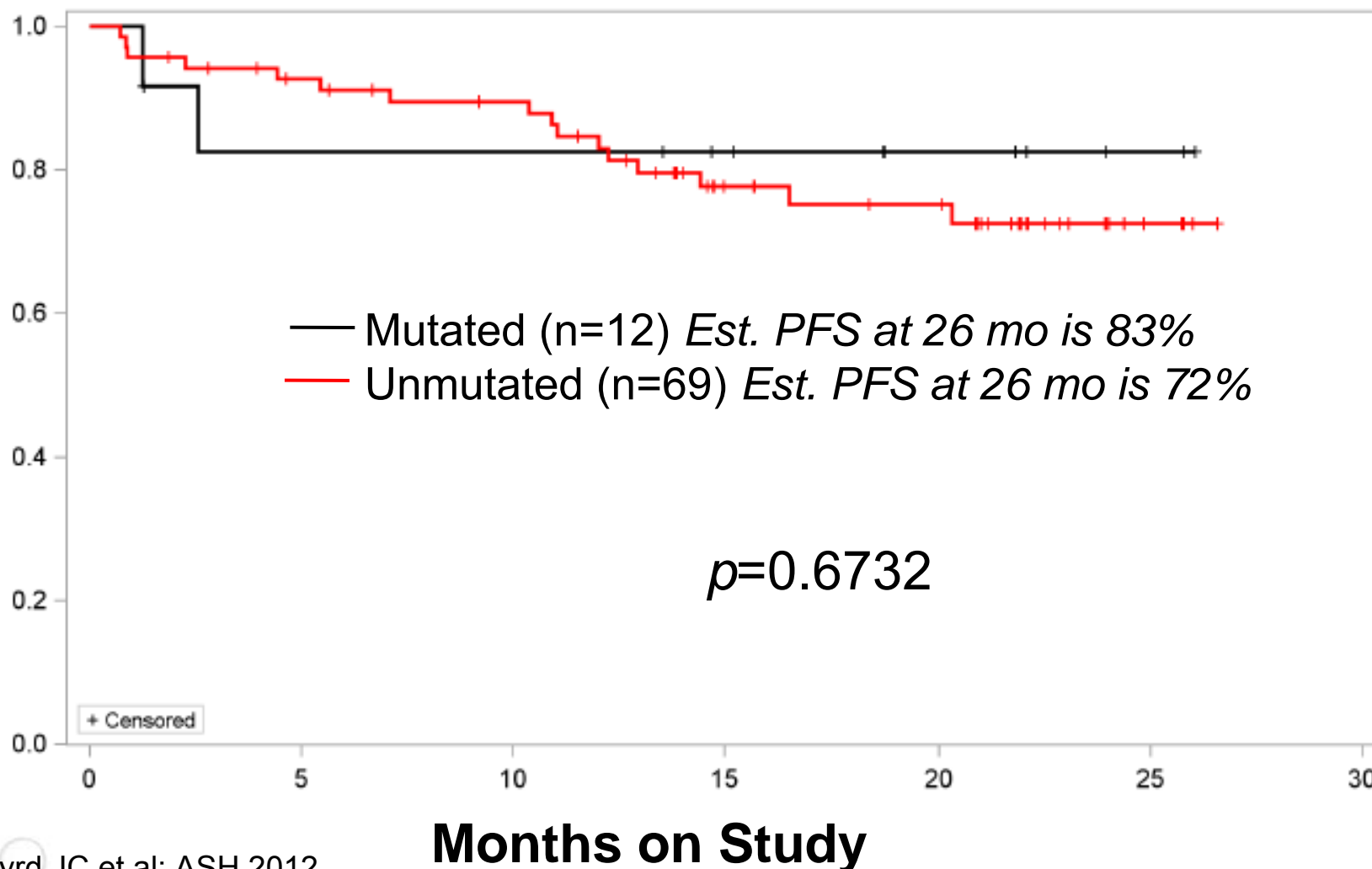
Progression-free Survival

PFS Probability



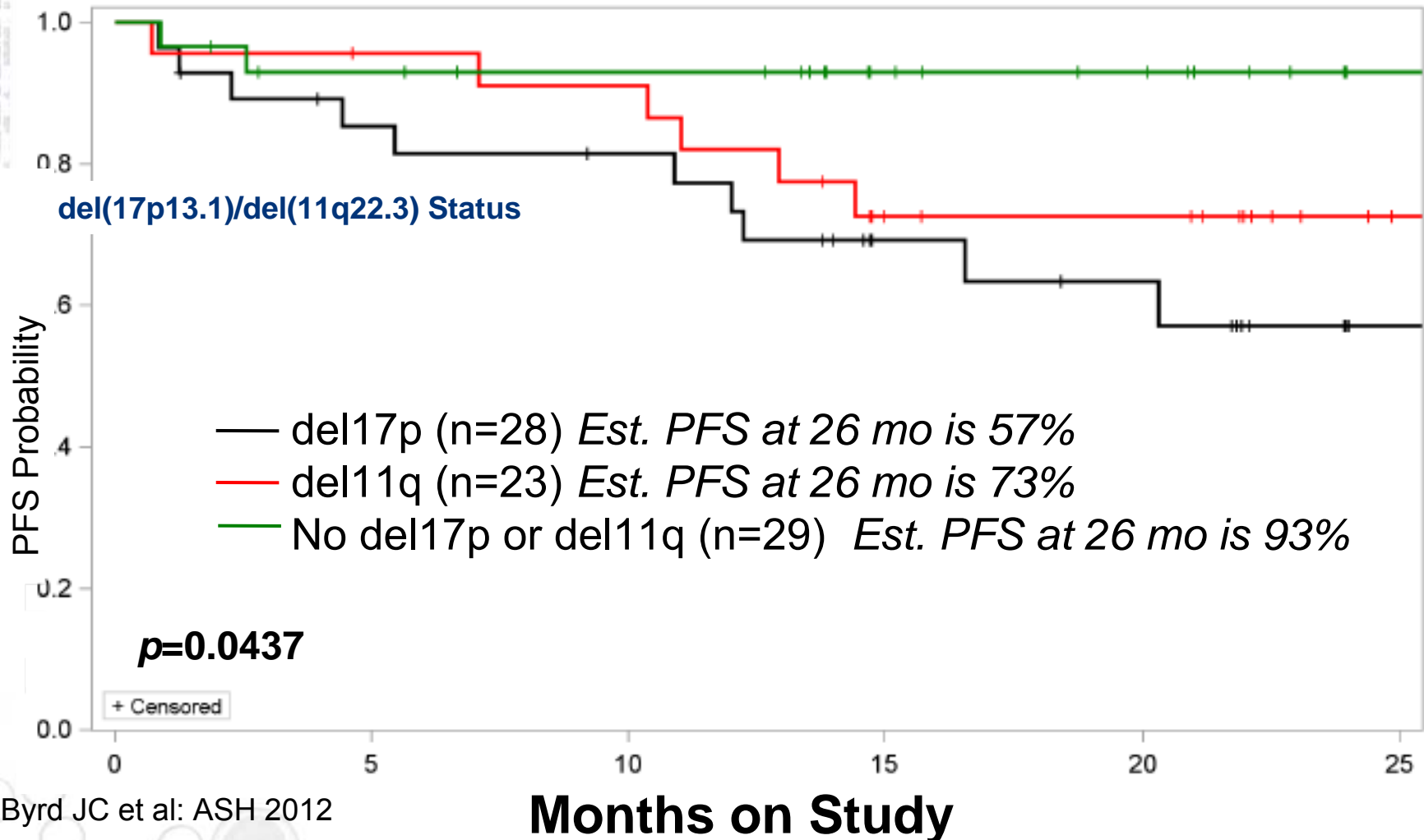
Byrd JC et al: ASH 2012

PFS by IGHV Mutational Status



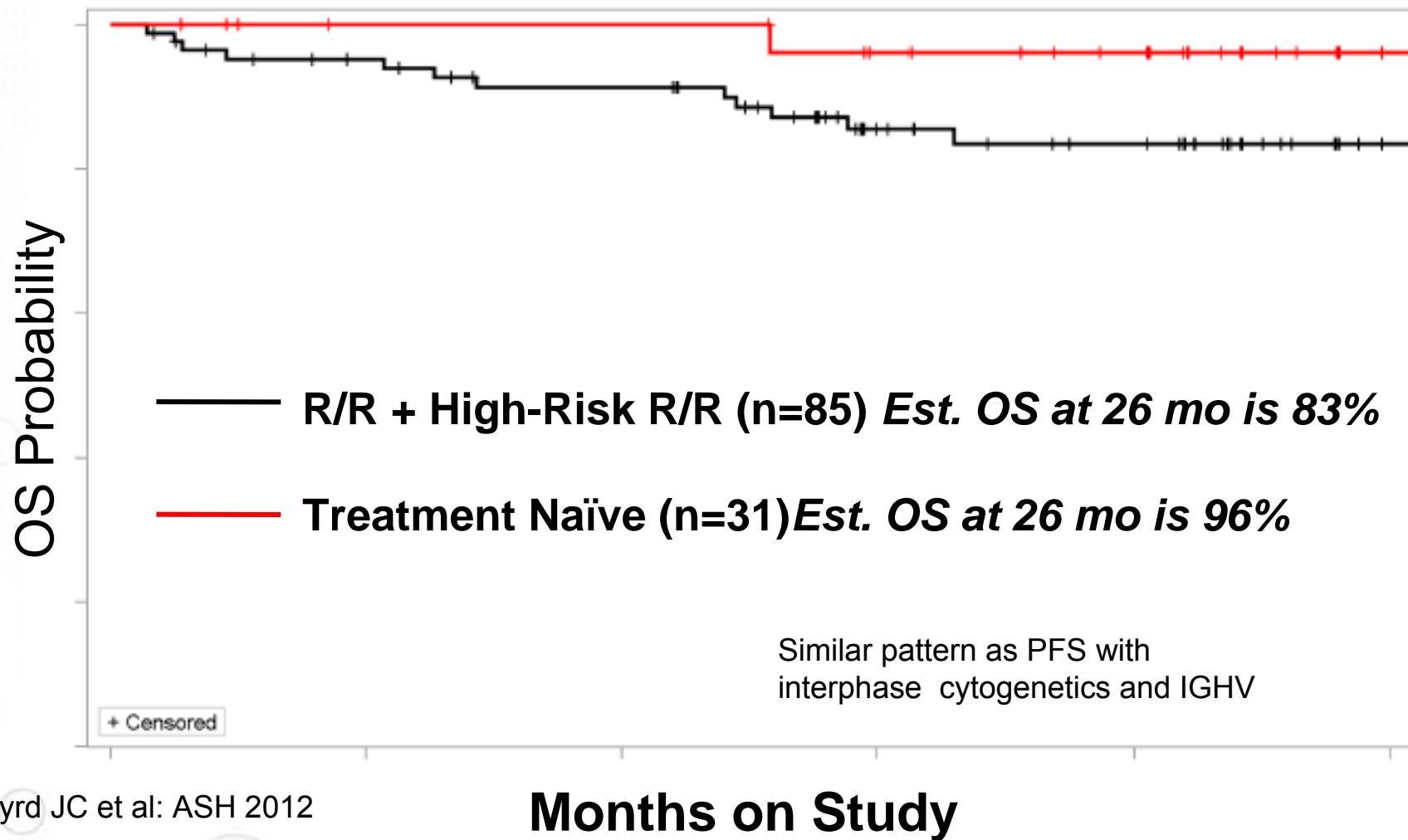
Byrd JC et al: ASH 2012

PFS by Interphase Cytogenetics



Byrd JC et al: ASH 2012

Overall Survival



Byrd JC et al: ASH 2012

Ibrutinib + Ofatumumab (PCYC 1109)

- Phase II study examining three sequences of ibrutinib + ofatumumab in relapsed CLL
- Cohort 1: Ibrutinib 420 mg/d until PD with delayed (day 29) ofatumumab using package insert schedule
- Demographics of pts include
 - Median age: 66 (range 51-85)
 - Median prior Rx: 3 (range 2-10)
 - % Rai III/IV: 50%
 - del(17p13.1): 37%
- ORR (100%, 4% CR) in patients heavily pre-treated relapsed/refractory CLL/SLL at 6 m evaluation

Jaglowski and Byrd ASCO 2012

Ibrutinib + BR (PCYC 1109)

- Multicenter phase I/II study of Bendamustine + Rituximab (x 6 cycles) + Ibrutinib (until PD) in relapsed and refractory CLL
- Demographics of patients include
 - Median age: 62 (41-82)
 - Median prior Rx: 2 (1-3)
 - % Bulky disease: 63%
 - Rai III/IV disease: 47%
 - % del(17p): 23%
 - % del(11q): 43%
- ORR (93%) with **13% CR (4 pts)** with 77% of patients still on study; 5 onto SCT and 2 with PD
- Toxicity similar to what observed with BR alone

S O'Brien and J Brown ASCO 2012

Summary of MRD Data with GS1101 and Ibrutinib in CLL

- Very few CR's seen with mono or combination Rx despite durable remissions obtained, particularly with ibrutinib in relapsed and refractory disease
 - Will differences in these treatment groups (MRD+ versus MRD- with time emerge?
 - Will response with MRD+ to MRD- conversion improve with further observation?
- New clinical trials under late planning in US Intergroup with ibrutinib will address this important question (Dr. Kay)
- MRD assessment should not be a mandatory expectation to agents already meeting traditional surrogate endpoints of PFS